hydration layers below ~4 water molecules are reached, the interaction potential turns rather insensitive to compression. The onset of transient (dynamic) clustering is envisaged in this concentration range. Our results also show that pressure suppresses protein nucleation, aggregation and finally crystallization in supersaturated condensed protein solutions. These findings are of importance for controlling and fine-tuning protein crystallization. Moreover, these results are also important for understanding the high stability of highly concentrated protein solutions (as they occur intracellularly) in organisms thriving under hydrostatic pressure conditions such as in the deep sea, where pressures up to the kbar-level are reached.

2617-Pos Board B47

Atomistic and Coarse-Grained MD Simulations of the Intrinsically Disordered Bacillus Subtilis Ribonuclease P Protein

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The Bacillus subtilis Ribonuclease-P (RNase P) holoenzyme is a protein-RNA complex; however, the protein becomes disordered in the absence of its RNA binding partner. To identify the main determinants of why the RNase P protein becomes disordered, we performed (i) a statistical analysis of its interactions to identify the critical minimally frustrated residues that are important for structural stabilization, (ii) atomistic MD simulations in the presence and absence of the osmolyte Trimethylamine N-Oxide (TMAO), which has been shown experimentally to stabilize its native structure even without its RNA binding partner, and (iii) coarse-grained Go-type MD simulations to determine the folding/unfolding mechanism. We observed an intermediate in our coarse-grained MD simulations that we propose is the partially disordered state in the absence of its RNA binding partner and the intermediate seen experimentally in TMAO-induced folding experiments. We also identified critical residues for stabilization that can be tested experimentally using standard mutagenesis folding kinetic experiments.

2618-Pos Board B48

The Dock-and-Coalesce Mechanism for the Association of Intrinsically Disordered WASP with the Cdc42 GTPase

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Intrinsically disordered proteins (IDPs) play key roles in signaling and regulation. Many IDPs undergo folding upon binding to their targets. We have proposed that coupled folding and binding of IDPs generally follow the dock-and-coalesce mechanism, whereby a segment of the IDP through diffusion docks to its cognate subsite and subsequently the remaining segments coalesce around their subsites [PCCP 14:10466(2012)]. Here we tested the validity of this mechanism on the association between the intrinsically disordered GTPase binding domain (GBD) of the Wiskott-Aldrich Syndrome protein (WASP) and the Cdc42 GTPase, by both experiment and computation. The association rate constants (ka) were measured by stop-flow fluorescence under various solvent conditions and temperatures. ka reaches 107 M-1s-1 at physiological ionic strength and has a strong salt dependence, suggesting that an electrostatically enhanced, diffusion-controlled docking step is rate-limiting. Diffusion control is supported by an inversely proportional relation between ka and the solvent viscosity with glucose as the viscogen. ka increases with increasing temperature; though the increase is larger than expected from the effect of temperature on the protein diffusion constants, the discrepancy may be accounted for by the effect of temperature in decreasing the solvent dielectric constant, leading to stronger electrostatic rate enhancement. Similarly, a modest decrease in ka by urea may be rationalized by the latter's effect in increasing the solvent dielectric constant. Our computation, based on the transient-complex theory [Structure 19:1744(2011)], identified the N-terminal basic region of the GBD as the docking segment, which has strong electrostatic complementarity with the cognate subsite. Our study suggests that the dock-and-coalesce mechanism allows WASP and other IDPs to code electrostatic complementarity into the docking segment to gain binding speed and use additional interactions formed by the coalescing segments to reinforce binding affinity.

2619-Pos Board B49

Cooperative Helix Formation in the (AAQAA)3 Peptide Obtained with the Drude Polarizable Force Field

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Molecular simulations can provide atomic-level details of protein folding. However, their accuracy is limited by approximations made in the underlying empirical force fields. Recently we presented a force field for peptides and proteins that includes explicit treatment of electronic polarization based on the classical Drude oscillator model.[1] The Drude force field was found to maintain protein native structures during microsecond molecular dynamics simulations of multiple folded proteins, and leads to significant variability of backbone and side chain dipole moments as a function of environment.[2] Here we report replica exchange simulations of the helix-forming $(AAQAA)_3$ peptide and the β-sheet-forming GB1 hairpin using this fully polarizable model.
Polarizable simulations of $(AAQAA)_3$ reveal the presence of folding cooperativity consistent with experimental observations. The cooperativity is significantly larger than that modeled by currently available non-polarizable force fields and is shown to be directly associated with enhanced dipole moments of the peptide backbone upon helix formation.[3] The GB1 hairpin is found to be less stable with the Drude force field compared to the experimental observation. Results from these extensive condensed phase simulations of peptide folding will be utilized, together with QM calculations of model alanine polypeptide systems, to further refine the backbone parameters in the Drude protein force field. In summary, our results demonstrate that the inclusion of explicit electronic polarizability leads to a fundamentally improved model of the physical forces dictating the structure and dynamics of polypeptides.

[1] P. Lopes, J. Huang, J. Shim, Y. Luo, H. Li, B. Roux, and A.D. MacKerell, *J. Chem. Theo. Comput.*, **2013**, *9*, 5430.
[2] J. Huang, P. Lopes, B. Roux, and A.D. MacKerell, *J. Phys. Chem. Lett.*, **2014**, *5*, 3144.
[3] J. Huang and A.D. MacKerell, *Biophys. J.*, **2014**, *107*, 991.

2620-Pos Board B50

Dependence of Internal Friction on Native Topology

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Apparent internal friction has been identified in the folding rates of several proteins and in the dynamics of unfolded proteins, via their dependence on solvent viscosity. Theoretical and computational studies have attributed this phenomenon, at least in part, to local barrier crossing events, in particular torsion angle isomerizations. However, there are still many systems for which no internal friction has been observed in experiment, and others for which the effect is only weak. Here, we elucidate the origin of this discrepancy by studying a model system whose native state can be either an α-helix or a β-hairpin. Remarkably, we find clear apparent internal friction for the helix, but no evidence of it for the hairpin. These results are consistent with the observation that proteins whose folding rates exhibit internal friction tend to be α-helical. We can explain the difference by examining the occurrence of torsional transitions along the folding coordinate of the hairpin and helix. Finally, we consider the folding of the Trp cage mini protein, whose structure includes both helical and hairpin elements. We obtain two barriers – the major barrier for formation of the hairpin and a minor barrier for initial helix formation, allowing us to dissect the contribution of internal friction to different parts of the energy landscape. We find a clear signature of internal friction for the helical barrier and, within the uncertainty of our calculation, little internal friction for the hairpin barrier. Our results show how variation of solvent viscosity can be used to probe features of folding mechanisms.

2621-Pos Board B51

Thermodynamics of β-Structures from Molecular Dynamics Simulations

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β-Sheets are some of the most common secondary structure motifs in proteins, and are important for mediating protein-protein interactions through their association. This association can also lead to the aggregation of misfolded proteins into β-pleated-sheets in neurodegenerative disorders like amyloidosis. The folding pathway from random coil to β-sheet usually involves two competing process: (1) the collapse of a hydrophobic core, and (2) the formation of intrapeptide hydrogen bonds. It has been proposed, and shown computationally, that the hydrophobic core collapse precedes hydrogen bond formation. In this study we examine the thermodynamics of β-hairpin formation for the GB1 domain of protein G with molecular dynamics simulations by calculating a two-dimensional free energy surface in both vacuum and explicit water using as our reaction coordinates (1) the radius of gyration of the hydrophobic core and (2) the number of native hydrogen bonds, corresponding to the two aforementioned folding processes, respectively. We also compare the results of different versions of the CHARMM force field, namely CHARMM22, CHARMM22/CMAP, CHARMM22* and CHARMM36. Finally, we show how these methods can be applied to other β-structures in vivo, namely β-helix structures in the outer membrane of Gram-negative bacteria.